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Function-Specific Neuropsychological Assessment

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INTRODUCTION

The purpose of neuropsychological testing, broadly speaking, is to define relationships between the integrity of the human central nervous system (CNS) and behavior, including cognitive processing as well as behavioral performance. Among long-term survivors of childhood and adolescent cancer, the most frequent scientific application of neuropsychological evaluation in the past 20 years has been to characterize the severity and pattern of late neurotoxicities by various malignancies, most frequently acute lymphoblastic leukemia (ALL) and brain tumors (BT), and their associated therapies, most often cranial radiation therapy (CRT) and systemic or intrathecal methotrexate (MTX). Because of the accumulated knowledge from neuropsychological studies, we are now able to identify subgroups of children who are at increased risk for neuropsychological impairments that are of a sufficient magnitude to limit their quality of life [1–4]. School-related problems are especially common [5,6]. These problems frequently include specific learning disabilities with underlying deficits in essential cognitive processing systems that limit the survivor's ultimate educational attainment and vocational level. Furthermore, because children's brains continue to develop through adolescence, there is likely to be a developmental emergence of deficits. The specific deficits detected at any given evaluation may be influenced by the child's age at the time of treatment and the timing of the neuropsychological assessment [5]. Based on our review of the existing literature and our personal experience, we have formulated guidelines for the clinical neuropsychological evaluation of high-risk subgroups of survivors of childhood cancer for school problems. The guidelines are a preliminary attempt to translate evidence-based research into practical recommendations for the practicing clinician.

The following guidelines are intended to provide general and function-specific guidelines for the most frequently referred cases, with the understanding that the low incidence and more complex cases may require extraordinary time and special techniques and expertise. These guidelines are not relevant to ''screening'' of unselected groups of survivors. They also do not define a comprehensive neuropsychological battery approach. Such approaches sometimes require 6–8 hours of direct patient contact and are used to evaluate children whose presenting complaints and histories do not readily suggest focused testing of specific functional abilities. Instead, our intent is to suggest an assessment strategy involving a 2–3 hour patient contact evaluation process that will give a picture of the patient's level of neuropsychological functioning as it relates to learning problems in school. In addition, we believe that it is important to have the results of this process used practically in the development of interventions to remediate or compensate for specific deficits that are identified.

The rationale for these guidelines is based upon projections that 1) a significant number of children surviving treatment for ALL and BT will become long-term survivors, 2) the incidence of significant learning problems will be high in particular subgroups, and 3) not all of these children will have access to psychologists who are necessarily experts in pediatric oncology or the neurotoxic risks associated with malignancies or their treatment. Therefore, the need exists for guidelines to facilitate and legitimize the referral process, to make essential information and expectations explicit to the psychological services provider, and to give the psychological services provider documentation to justify an evaluation if the necessity of services is questioned by a third-party payer. The importance of developing and validating evidence-based guidelines within subspecialty areas of oncology has recently been emphasized elsewhere [7].

These guidelines make several other assumptions. 1) The patient has been referred for evaluation because of a suspicion that a neuropsychologic or neurologic problem is impairing school-related performance, 2) the patient and family are motivated to participate in the evaluation

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TABLE I. Proposed Guidelines for the Assessment of School Problems

1.0 History by medical chart review and patient/parent interview
1.1 Prenatal
1.2 Developmental
1.3 School
1.4 Parental/sibling school/occupational
1.5 Previous school interventions
2.0 Medical diagnosis and treatment history
2.1 Young age as a pervasive risk factor
2.2 Chemotherapy
2.2.1 Methotrexate (MTX)
2.2.2 Cisplatinum
2.3 Cranial radiation therapy (CRT)
2.3.1 Total dose, field, volume, fractionation
2.3.2 Interval since treatment
2.4 Neurosurgical procedures (brain tumors)
2.4.1 Tumor location, volume, invasiveness
2.4.2 Acute and chronic central nervous system complications
2.4.3 Shunts
3.0 Current medical status
3.1 Physical symptoms and complaints
3.2 Neurological problems
3.2.1 Vision and hearing
3.2.2 Seizures
3.3 Current medications
4.0 Psychological testing
4.1 Intellect and achivement
4.2 Personal-social adjustment
4.3 Function-specific tests
4.3.1 Manual dexterity and visual-motor skills
4.3.2 Attention and processing speed
4.3.3 Learning and memory

process, 3) the patient will be evaluated by a licensed clinical psychologist with competence in clinical child or pediatric psychology if not pediatric neuropsychology, and 4) the patient's treating physician and/or medical record are available to the examining psychologist.

GUIDELINES

The Guidelines for Assessment of School Problems are presented in Table I. The following annotations are coded numerically to match corresponding sections of the Guidelines.

1.0 History by Medical Chart Review and Patient/Parent Interview

A thorough clinical history and knowledge of the patient's disease and therapy enhances the ability to interpret the significance of psychological testing results.

1.1 We are unaware of data that indicate that prenatal complications are more common among children who are diagnosed later with ALL or BT. However, if they are present but not acknowledged, then these can complicate interpretation of testing results.

1.2 The developmental history is essential for hypotheses about the patient's pre cancer learning capacity. Cumulative insults and other risks for learning problems (e.g., head trauma, lead levels, otitis media) may combine to determine individual thresholds for neuropsychological symptoms [8].

1.3 It is especially pertinent to note the frequency of school absences and the potential impact of these on the patient's ability to acquire academic skills at an age-appropriate rate. Estimates for children receiving treatment for cancer vary from 16 days to 40 days per year compared with 10 days for siblings [9,10].

1.4 The educational and occupational attainments of siblings and parents are a useful measure of the patient's probable psychoeducational ''trajectory'' if he or she had not been diagnosed with cancer. Psychoeducational studies of children with cancer often use sibling controls for this reason [9,11].

1.5 Previous attempts to provide intervention for a learning problem, either through special education services, medication (e.g., methlyphenidate), or tutoring, validate the severity of the problem, and also provide information about the relative efficacy of these interventions.

2.0 Medical Diagnosis and Treatment History

CNS disease and treatment factors present a variety of potential insults to the learning capacity of the school-aged survivor of ALL or BT. Often, chronic neuropsychological effects are delayed in their appearance either because of delayed biological damage or because of adverse effects on a new skill or ability area that will not normally emerge until sometime after treatment completion. Generally speaking, risk increases with the aggressiveness of the therapy provided to the CNS, making children with BT at greater risk than those with ALL [3].

2.1 No other single risk factor has been found to be more important than a young age at the time of CNS therapy. Although risk is probably distributed on a continuum and is correlated inversely with age, children under the age of 4 years and especially those under the age of 2 years are at high risk for later impairment [3]. Damage to the immature brain, especially to the formation of myelin sheaths of axons, has been associated with a specific developmental pattern of deficits [5,12]. Assessment and intervention strategies must be based on expectations of newly emerging skills and abilities with maturation.

2.2 It is not yet known whether the onset and pattern of neuropsychological deficits induced by MTX are different from those induced by CRT and whether these differences may be influenced by gender [10,13]. Cisplatinum and CRT may both cause a dose-dependent, sensorineural hearing loss that begins at high frequencies and progresses to speech frequencies with continued exposure [14].

2.3 Risk for late complications of CRT increases with

TABLE II. Proposed Requirements for Practice Standards, Practice Guidelines, and Practice Options in Choosing Psychological Tests*

Requirements for ''practice standards''
- 1.1 The test has a *high degree* of general clinical acceptance with *overwhelming* scientific evidence of usefulness in the evaluation of children surviving ALL and BT, and
- 1.2 The test is published and has developmental norms appropriate to the age range of ALL and BT, and
- 1.3 Evidence of validity with ALL or BT survivors (>2 years from completion of therapy) from one or more publications in a peer-reviewed journal that the test:
  - 1.3.1 Discriminates between patients and normal controls (not just test norms), or
  - 1.3.2 Discriminates between subgroups of patients with known different risks of impairment, or
  - 1.3.3 Demonstrates sensitivity to change in process over time among a sample of patients, or
  - 1.3.4 Correlates with abnormalities of the brain seen on CT/MRI.

2.0 Requirements for ''practice guidelines''
- 2.1 The test has at least *some* general clinical acceptance and *some* scientific evidence of usefulness in the evaluation of children surviving ALL and BT, and
- 2.2 Criteria 1.2 and 1.3 under practice standards

3.0 Requirements for ''practice options''
- 3.1 The test has *some* general clinical acceptance with *unknown* usefulness in the evaluation of children surviving ALL and BT, and
- 3.2 The test purports to assess cognitive processing abilities that appear relevant to learning problems of the school-age child after treatment for ALL or BT

*ALL, acute lymphoblastic leukemia; BT, brain tumor; CT/MRI, computed tomography/magnetic resonance imaging.

the magnitude of the total dose, fraction per dose, volume of brain treated, and time elapsed from treatment [15]. Among children treated for medulloblastoma, the most common malignant brain tumor of childhood, intellectual decline, may continue 10 or more years from treatment [16].

2.4 Access to a report of a recent neurological examination of the patient is essential, in part because neurological deficits following neurosurgery are predictive of later neuropsychological problems [16]. The ''posterior fossa syndrome'' is characterized by mutism following surgery involving the cerebellum [17]. Some children will have had long-standing and undetected increased intracranial pressure prior to shunting: These children are at risk for cerebral damage, such as mesial temporal lobe atrophy and associated memory deficits, as well as visual impairment secondary to optic atrophy [18].

3.0 Current Medical Status

This algorithm assumes that children have completed their anticancer therapy, so that acute and subacute side effects are no longer an issue. However, children surviving ALL and BT may require continuing medications for complications of their malignancy or its treatment long after anticancer therapy has been terminated.

3.1 Some children treated for cancer, especially those given head and neck irradiation, may have previously undetected hypothyroidism with chronic fatigue and problems with attention and concentration [19].

3.2 The ability of children to adapt or compensate for neurological deficits is impressive. Sometimes, their adaptation disguises the true extent of the problem, especially for less noticeable deficits, such as those relating to vision (decreased acuity or visual fields) or hearing, which nevertheless may affect testing results and the ability to function in the classroom. The management of seizures and headaches may be problematic among children treated for BT, with some anticonvulsants (e.g., phenobaribital) having adverse effects on learning [20].

3.3 Many children treated for malignant brain tumors will be placed on partial or total hormone replacement therapies. These include testosterone, growth hormone, synthroid, and other drugs, some of which must be maintained at an optimal level to avoid physical and mental symptoms [21].

4.0 Psychological Testing

The following classification of tests into ''practice standards,'' ''practice guidelines,'' and ''practice options'' is modeled after a recent publication on the diagnosis of Lyme disease published by the American Academy of Neurology [22]. Within this framework, standards, guidelines, and options represent categories of recommendations for practice in decreasing order of scientific evidence and clinical acceptance for survivors of ALL and BT (Table II). The present classification is preliminary and remains to be confirmed by review of an expert panel.

From 1975 through 1995, 80 studies of neuropsychological or psychoeducational testing of survivors of ALL and BT were identified in peer-reviewed journals published in English. We divided the papers into those that included tests of intellect and achievement, personal-social adjustment, and those that included more narrowly focused, function-specific tests. Function-specific tests were further divided into the most commonly occurring categories: manual dexterity and visual-motor skills, attention and processing speed, and learning and memory

[5]. Of the 80 papers that were reviewed, 22 utilized function-specific tests that appear to be useful in defining the learning problems of survivors. The remaining 58 papers included only tests of intellect and achievement without interpretation of underlying processing factors or failed to demonstrate statistically significant effects on the function-specific tests that were chosen for analysis. Finally, some studies that would otherwise qualify used function-specific tests that were obscure, not easily obtainable by the clinician because of a primary research intent, or lacked any available normative information.

4.1 Intellect and Achievement

A. Practice standards.

Wechsler Intelligence Scales. Numerous empirical studies have documented the validity of the various age-appropriate Wechsler Intelligence Scales [23–25] in the evaluation of survivors of ALL and BT. Recent reviews provide the best initial source for primary references [1–6].

Wide-Range Achievement Tests. Like the Wechsler Scales, the Wide-Range Achievement Tests [26] are the most substantiated tests of academic achievement difficulties among children surviving ALL or BT. They provide a brief screening of reading (word recognition), spelling, and computational mathematics. Recent reviews provide the best initial source for primary references [1–6].

B. Practice guidelines.

C. Practice options.

Wechsler Individual Achievement Test [27].

Woodcock-Johnson Revised Tests of Achievement. [28]

4.2 Personal-Social Adjustment

A. Practice standards.

B. Practice guidelines.

Child Behavior Checklist. The Child Behavior Checklist [29], a parent-report inventory of childhood adaptive functioning (social, school, activities) and behavioral problems (internalizing, externalizing), has received significant validation with children surviving both ALL and BT [30–33]. It is important to use care when interpreting scales that include items related to physical complaints, because these may be reflective not of behavior problems but of the reality of the symptoms experienced as a result of disease and treatment [34].

C. Practice options.

4.3 Function-Specific Tests

4.3.1 Manual dexterity and visual-motor skills.

A. Practice standards.

B. Practice guidelines.

Finger Tapping. The Finger Tapping [35] or Finger Oscillation Test requires the patient to tap a telegraph key with the index finger of each hand on timed trials. It has been validated as a useful measure of motor speed among children with ALL [36–40]. We are unaware of similar studies with BT survivors and these are certainly needed.

Developomental Test of Visual Motor Integration. The Developmental Test of Visual Motor Integration (VMI) [41] requires the patient to copy increasingly difficult geometric figures from samples in an untimed format. Validation studies are available for both ALL and BT survivors [37,42–44].

Detroit Test of Learning Aptitude (motor domain) The Detroit Test of Learning Aptitude (motor domain) [45] contains 11 subtests of specific mental abilities that are collapsed into six composite domain scores, one of which is the motor domain, which involves tasks measuring complex manual dexterity. It has received some evidence of validity in the assessment of children with ALL [10].

C. Practice options.

Grooved Pegboard. This test requires the patient to place pegs with a ridge along one side into slotted holes in a timed format: Each hand is tested separately. Normative data are inadequate: Sources vary by investigator and are not easily available to clinicians. However, research studies with internal control groups have demonstrated significant findings [37,38,42,43].

Rey-Osterrieth Complex Figure. This test requires the patient to copy a complex geometric figure: It is scored for accuracy and time to completion. Materials are not commercially available and must be constructed by the user: Normative data are inadequate. However, several research studies with internal control groups have demonstrated significant findings [46–51].

4.3.2. Attention and Processing Speed

A. Practice standards.

B. Practice guidelines.

Trail-Making Test (forms A and B) Trails form A requires the patient to connect numbers sequentially, whereas Trails form B requires alternating between numbers and letters: Both are timed [35]. Evidence with ALL and BT patients shows significant deficits in a variety of study settings [10,37,38,52,53].

Detroit Test of Learning Aptitude (attention domain). This test contains 11 subtests of specific mental abilities that are collapsed into six composite domain scores, one of which is the attention domain [45], which involves tasks measuring concentration, attending, and short-term memory. It has received limited validation among children surviving ALL [10].

C. Practice options.

Altered Reaction Time. Both auditory and visual stimuli have been used to elicit reaction times. Materials and protocols vary by investigator and normative data are

inadequate. Nevertheless, several investigators of the late cognitive effects of ALL have found differences among groups related to treatment [46,47,54].

Processing Speed Factor (WISC-III) [24].

Conner's Continuous Performance Test [55].

Test of Variables of Attention [56].

IVA Continuous Performance Test [57].

Processing Speed Cluster, Woodcock-Johnson Revised Tests [58].

4.3.3 Learning and Memory

A. Practice standards.

B. Practice guidelines.

Learning Efficiency Test. The Learning Efficiency Test [59] is an untimed test of visual and auditory memory that is scored for immediate, short-term, and long-term recall. Performance is also scored with and without regard to the correct sequence of recall. It has been validated in one study of ALL patients and in one study of BT patients [60,61].

Distractibility Factor (WISC-III). This composite score is derived from the WISC-R or WISC III [24], but we have not differentiated between the two forms here. Several studies have validated the independent interpretation of this factor score to identify deficits in ALL survivors [38,40,42,43,54,62].

Wechsler Memory Scale. The Wechsler Memory Scale [63] has been used with young adult and adult survivors of ALL and BT with some success in defining memory deficits [46–48].

C. Practice options.

Rey Auditory Verbal Learning Test. The patient is read a list of words and is asked to repeat them back orally at the end of the list. The same words are repeated over several trials, and the number correct are scored on each trial, generating a ''learning curve.'' Materials are not commercially available and must be constructed by the user: Normative data are not adequate. Nevertheless, several studies of survivors of ALL using control or comparison groups have identified memory problems on this measure [46,47,49,50].

Rey-Osterrieth Complex Figure. In addition to the copying format, this test also includes a memory format whereby patients are asked to draw the figure after the passage of time. Materials are not commercially available and must be constructed by the user, administration protocols vary by investigator, and normative data are inadequate. Nevertheless, several studies of children surviving ALL and BT have found significant nonverbal memory deficits compared with internal control or comparison groups [46–51].

Selective Reminding Test. This test is also known as the Buschke Selective Reminding Test. This test of memory has verbal and nonverbal forms and generates a learning curve similar to the Rey Auditory Verbal Learning Test. The primary difference is that only those words or figures that are not recalled are repeated prior to the next trial. It is not commercially available, and normative data are not easily available: Administration protocols vary by investigator. Some evidence of validity is available for samples of children surviving ALL [37,42,54].

Goldman-Fristoe-Woodcock Auditory Memory Tests. The Goldman-Fristoe-Woodcock Auditory Memory Tests [64] include tests of recognition memory, content memory, and sequence memory. Unfortunately, it is out of print, and only the forms are currently available from the publisher. It does have some evidence of validity in identifying memory deficits among survivors of BT [65].

California Verbal Learning Test [66,67].

Wide-Range Assessment of Memory and Learning [68].

Benton Visual Retention Test [69].

Children's Memory Scale [70].

DISCUSSION

The present clinical guidelines for the neuropsychological assessment of survivors of ALL and BT for school-related problems are preliminary and will require confirmation from an expert panel as well as periodic revisions as more research is published that validates new tests and techniques for this purpose. Although major controversies persist regarding the relative adverse effects of different combinations of CRT and chemotherapy to the developing CNS, we are presently able to define several primary cognitive processes that are damaged by similar treatments. The severity of damage to these processes may result in syndromes ranging from global mental retardation to only subtle or focal changes. At least mild processing problems are expected in many survivors, especially for those who are treated for BT, with some deficits not expected to emerge until years later [5]. Therefore, surveillance of high-risk but asymptomatic children is justified.

It is important, as the health care delivery system evolves in the United States, to ensure that psychological healthcare providers who do not have experience in pediatric oncology are educated with regard to the risks for learning problems among survivors of childhood cancer, the most likely patterns of test findings that will be exhibited, and which tests are best validated for this purpose. We have also attempted to provide appropriate cautions and explanations for unexpected complications in the testing process. Finally, it is hoped that this document can assist psychological service providers in justifying their services and the time and techniques employed if these are ever questioned in the process of reimbursement by a third party.

The present guidelines provide an evidence-based

framework for clinical decision making and test selection in the evaluation of long-term survivors with school-related problems. We encourage confirmatory studies of tests that are now categorized as Practice Guidelines or Practice Options as well as exploratory studies of new tests so that a greater variety of tests with a more comprehensive scope can be justified.

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